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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,166	04/04/2001	Frederique Ahne Le Gal	102,174	2214

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,166	LE GAL ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/12/06 & 10/11/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,28-31,35-39,41 and 43* is/are pending in the application.

4a) Of the above claim(s) *41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,28-31,35-39 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/06 has been entered.

Applicant's amendment filed on 10/11/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 23-40 and 43), and species of dipalmitoyl lysyl as the lipid moiety, TT 830-843 as the T_{aux} cell epitope, amino acid residues 20-34 of SEQ ID NO: 276 as the CTL epitope, *i.e.,* FPVTPQVPLRPMTYK, and the spacer RGR in Applicant's reply filed 1/6/04.

Claim 41 (non-elected group II) remains withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 23, 28-31, 35-39 and 43 are currently being examined.

3. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the brief description of the drawings for Fig. 5, *i.e.,* Figure 5 discloses two peptide sequences). The Examiner notes Applicant's remark in the amendment filed 8/5/06, *i.e.,* that Applicant filed a sequence listing on 8/27/03 and that the two sequences are SEQ ID NO: 9 and 11. However, Applicant is still required to amend the specification at the Brief Description of the Drawings for Figure 5 to recite the SEQ ID NO.

4. The disclosure is objected to because of the following informalities:

The use of the trademarks VYDAC (page 11 at line 18) and ZORBAX (page 11 at line 18) have been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23, 28-31, 35-39 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amended material not supported by the disclosure and claims as originally filed is as follows: (1) the amendment of base claim 23 at the second to last line to recite "at least one aminoacid spacer chain selected from the group consisting of GLY ARG and ARG GLY ARG," (2) the amendment of base claim 23 to recite "or two distinct epitopes are separated by a hydrophilic amino acid spacer chain selected from the group consisting of GLY ARG and ARG GLY ARG". The said amendment opens the claim to read upon the inclusion of more than one amino acid spacer chain between the lipid moiety and the epitopes and between the epitopes, *i.e.,* Gly Arg Arg Gly Arg or Arg Gly Arg Gly Arg with regard to (1), and with regard to (2), the claim amendment places separation by spacer chains in the alternative for a linker present either between the lipid moiety and the epitopes ***or*** between the epitopes. The original disclosure (originally filed claim 3) is "at least one of the spacers has one of the following sequences: Gly Arg or Arg Gly Arg," and "characterized in that the epitopes and the lipid portion on the one hand and the epitopes on the other hand are independently separated by amino-acid sequences, so-called spacers...".

7. Claims 23, 28-31, 35-39 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a lipopeptide and vaccine thereof, comprising "one lipid moiety" and "at least one CTL epitope consists of a CTL epitope of a HIV protein", "at least one auxiliary T epitope" and spacer(s), and a vaccine comprising said lipopeptide, and wherein the lipopeptide and vaccine comprising said lipopeptide is used for prophylaxis or treatment. The specification has not enabled the breadth of the claimed invention because the claims encompass lipopeptides comprising a lipid or portion thereof recited in instant base claim 1, and use prophylactically as a vaccine or for treating AIDS. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed lipopeptide/composition thereof can be made and used prophylactically or for treatment. The specification discloses no working examples with regards to the use of

the instant invention for prevention of disease *in vivo*, specifically for prevention of HIV, nor for treatment of AIDS.

The disclosed use for the claimed lipopeptide/vaccine thereof is for the production of a medicine or a vaccine effective as a preventative or a curative by means of *in vivo* generation of CTL (page 1 at lines 14-15 and page 7 at lines 5-19). The specification further discloses that the lipid portion of the lipopeptide can comprise one or several optionally branched or [u]insaturated chains derived from C10-C20 fatty acids or a steroid, linolenic, 2-aminohexadecanoic acids, pimeluatide or trimexautide (especially page 5 at lines 19-32). The specification discloses that the lipid portion may be made of or comprise a moiety of palmitic, oleic, linoleic, linolenic, 2-aminohexadecanoic acids, pimelautide or trimexautide (especially page 5 at lines 30-32).

The specification does not disclose any lipopeptide used prophylactically as a vaccine to treat a condition.

Evidentiary reference the Merck Manual (of record) teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease. Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

With regard to "vaccine," the term by definition implies any preparation intended for active immunological prophylaxis; *e.g.*, preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease.

The specification discloses that a NEF epitope amino acid residues 73-82 induces a strong specific CTL response in HLA-A3 transgenic mice, and that the TT-NEF monopalmitoyl lipopeptides were able to induce a CTL response as high as the NEF 73-82 epitope (page 24 at lines 16-19). The specification further discloses that three HLA-A2 binding epitopes Gag 77-85, Pol 476-484 and Pol 346-354, induced a low specific CTL response in HLA-A2 transgenic mice, but the corresponding monopalmitoyl lipopeptides were able to induce a higher immune response (page 24 at lines 10-14).

There is insufficient evidence that such a study would correlate with *in vivo* efficacy in humans. It is well known in the art that retroviral therapies, especially HIV therapies, are refractory to anti-viral therapies (see Fahey *et al.,* Clinical Experimental Immunology, 1992; Letvin, Science, 1998). The obstacles to developing a successful therapy of HIV are well documented in the literature. These obstacles include 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with the respect to the gene encoding the envelope protein. 2) The fact that the mode of viral transmission includes both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission. 3) The establishment of a latent viral infection. 4) The ability of the virus to evade the immune responses in the central nervous system due to the blood-brain barrier. 5) The complexity and variation of the pathology of HIV infection in different individuals. 6) The inability of a natural infection to one strain of HIV to protect an individual from being infected with another strain of HIV (Machuca *et al.* Intervirology 1998, see discussion). These obstacles establish that the contemporary knowledge in the art would not allow one of skill in the art to use the claimed vaccine to treat and/or prevent HIV infection without undue experimentation. Furthermore, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Applicants have not provided any convincing evidence that their claimed lipopeptide and vaccine is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance in to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence in light of the high degree of unpredictability in the art regarding which structural features are required in order to provide treatment or protection, the absence of working examples directed to the same, and the complex nature of the invention, the specification fails to provide an enabling disclosure.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 1/12/06 have been fully considered, but are not persuasive.

Applicant's arguments are of record on pages 7-9 of Applicant's said amendment, briefly: (1) lipopeptides comprising the mono-palmitoyl derivatives are the most efficient lipopeptides, (2) the Levy *et al* reference (Aids, 2005, Vol. 19(3), pages 279-286) submitted by Applicant in the IDS filed 1/12/06 underlines the *in vivo* efficacy of the claimed lipopeptides for therapeutic immunization of HIV-1-infected patients.

It is the Examiner's position that: (1) the ability of mono-palmitoyl derivatives to increase the immune response against four HIV epitopes in transgenic mice does not speak to the issue of treating or preventing AIDS, (2) the Levy *et al* reference states "The long-term clinical benefit of therapeutic immunization in HIV infection is still not demonstrated...although there is as yet no consensus upon criteria for the clinical efficacy of therapeutic immunization, the capacity to stimulate HIV-specific immune responses and to control HIV replication after treatment interruption in chronically infected patients *might* [Examiner emphasis] be promising...We believe that these findings would help in the *development* [Examiner emphasis] of therapeutic immunization strategies in the treatment of HIV disease, and also in other chronic viral diseases." Thus, the Levy *et al* reference indicates that therapeutic immunization has not demonstrated a clinical benefit to date, and that their findings might help in the development of immunization strategies for treatment of HIV disease.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 28-31 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 28 and 29 are indefinite in the recitation of "amino acid spacer chain comprises an alkyl functionalized by a thiol and non-peptide bonds" or "amino acid spacer chain comprises a member selected from the group consisting of thiazolidine, oxime and hydrazone," respectively, because it is not clear what is meant. Base claim 23 recites a spacer chain that consists of Gly-Arg or Arg-Gly-Arg, so that the said spacer chain can not "comprise" additional components recited in instant claims 28 and 29.

b. Claims 30, 31 and 35 recite the limitation "lipid." This limitation lacks antecedent basis in base claim 23 which recites "lipid moiety."

10. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.*, 4/4/01, in light of Applicant's amendment of base claim 23 to add new matter as enunciated at item #6 above. In addition, Applicant is reminded that an English language translation of the foreign priority document FR 98 04323 filed 4/7/98 has not been provided.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 23, 28-31, 35-39 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/51630 (publication of PCT/FR99/00792, translation of the claims). Although WO 99/51630 was published in French, the Examiner has provided a translation of the claims obtained from the EPO Online Public File Inspection.

WO 99/51630 teaches a lipopeptide comprising a T_{aux} epitope that is tetanus toxoid 830-843 or PADRE, at least one CTL epitope from an HIV protein (and also an embodiment with two CTL epitopes), and a lipid moiety consisting of an unbranched or branched, saturated or unsaturated chain derived from fatty acids of C_{10}-C_{20}, including from the lipid moieties recited in instant claim 35, and wherein the lipopeptide and all the epitopes are separated by a linker at least one of which is Gly-Arg or Arg-Gly-Arg, and including wherein the spacer chain may comprise the limitations recited in instant claims 28 and 29, and wherein the non-lipid portion is comprised of 15 to 100 amino acid residues, and a vaccine composition comprising said lipopeptide (see claim translation of WO 99/51630, especially claims 1-9, 12-17, 20 and 21).

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 23, 30, 31, 35-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 (of record) in view of EP 0346022A1 (of record), Rammensee *et al* (Immunogenetics 1995, 41: 178-228, of record), BenMohamed *et al* (Eur. J. Immunology 1997, 27(5): 1242-1253, of record), U.S. Patent No. 5,935,824 (of record) and Skidgel (Meth. Enzymol 1995, Vol. 248, pages 653-663).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-843 QYIKANSKFIGITE or the Th epitope PADRE peptide to CTL epitopes will also increase immunogenicity, and (3) teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16, page 18 at lines 18-21). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain consisting of GR.

EP 0346022A1 teaches an HLA-B27 restricted CTL epitope containing peptide from HIV (gag p24 265-274, KRWIILGLNKIVRMY) that can be incorporated into a vaccine against HIV, either alone or in the form of a fusion protein containing other epitopes (entire article, especially abstract, summary of the invention and claims).

Rammensee *et al* teach the minimal CTL epitope HIV-1 gag p24 265-274 (*i.e.*, KRWIILGLNK, a subsequence of that taught by EP 0346022A1 above), as well as other HIV epitopes restricted by HLA-B27 or by other class I molecules, including non-hydrophilic peptides such as SFNCGGEFF HIV gp 120 amino acid residues 380-388 (especially Table 3 on page 200, page 209, page 210, pages 193-198).

BenMohamed *et al* teach that incorporating a simple palmitoyl-lysine chain in a peptide from an infectious agent that contains Th and CTL epitopes can dramatically increase Th and CTL responses (especially abstract).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

Skidgel teaches Gly-Arg is a substrate of human plasma carboxypeptidase N (especially Table II on page 662, abstract and paragraph spanning pages 653-654).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an HIV CTL epitope as taught by US Patent No. 5,935,824 and by Rammensee *et al* in place of the CTL epitope in the peptide taught by WO 95/19783 A1 comprising a palmitic acid moiety such as the palmitoyl chain taught by BenMohammed *et al* and to have created a hydrophilic spacer comprising Arg as disclosed by US Patent No. 5,935,824 by adding Arg to the Gly taught by WO 95/19783 A1 between the Th and the CTL epitope and in between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1, to create the Gly-Arg recognition sequence taught by Skidgel, and to have made a vaccine as taught by EP 0346022A1 comprising the lipopeptide. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have interposed a linker between the CTL epitope and a second CTL epitope if one was used as per the teaching of EP 0346022A1, in order to avoid creating a neo-epitope or destroying an existing epitope.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to improve the efficiency of immunization of the HIV CTL epitope taught by Rammensee *et al* and by EP 0346022A1 by using a lipopeptide such as the one taught by WO 95/19783 A1 but with the said HIV CTL epitope, since WO 95/19783 A1 teaches that adding a multivalent auxiliary Th epitope and a lipid such as palmitic acid increases immunogenicity, and BenMohammed *et al* teach that use of a single palmitoyl chain can dramatically increase immune response to a peptide containing T and B cell epitopes, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Lys or Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, *i.e.,* will be cleaved, Skidgel teaches that Gly-Arg is a recognition sequence for human plasma carboxypeptidase N, and WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution because the lipid moiety is hydrophobic as was known to one of ordinary skill in the art at the time the invention was made, and even more particularly when the T cell epitope is non-hydrophilic such as the one taught by Rammensee *et al*.

15. Claims 23, 30, 31, 35-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 in view of Deprez *et al* (Vaccine, 1996, 14(5): 375-382, of record), Berzofsky *et al* (J. Clin. Invest, 1991, 88: 876-884, of record), EP 0346022A1 (of record), Rammensee *et al* (Immunogenetics 1995, 41: 178-228, of record), U.S. Patent No. 5,935,824 (of record) and Skidgel (Meth. Enzymol 1995, Vol. 248, pages 653-663).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-843 QYIKANSKFIGITE or the PADRE peptide, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3) teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain consisting of GR.

Deprez *et al* teach HIV env peptides that contain class I and class II epitopes, *i.e.,* CTL and antibody epitopes, linked to trimexautide or palmitic acid or dexadecanoic acid or cholesterol, *i.e.,* single lipid moieties. Deprez et al further teach a 41-mer chimeric lipopeptide made by collinear synthesis of three sequences from influenza NP protein containing three CTL epitopes. Deprez *et al* teach that each epitope was restricted to a different haplotype, *i.e.,* to a different class I MHC molecule, and that provided a concomitant stimulation of specific Th cell responses were achieved, a CTL response could be elicited to all three epitopes (see entire article, especially, abstract, introduction, peptide synthesis section of materials and methods, figure 1, discussion).

Berzofsky *et al* teach construction of peptides encompassing multideterminant clusters of HIV env protein (*i.e.,* large peptide subsequences of HIV env protein that contain overlapping or contiguous CTL epitopes restricted by different HLA or MHC class I molecules) to induce *in vitro* T cell responses in mice and humans of multiple MHC types. Berzofsky *et al* teach that these peptides may be useful components of a vaccine due to their broad recognition by from 52-73% of outbred, HLA-diverse infected human donors. Berzofsky *et al* teach that these peptides by themselves do not constitute a complete vaccine, and that vaccines are known to elicit antibodies and Th cells as well as CTL, that it is desirable that a synthetic vaccine elicit all three major arms of the immune response (especially abstract, introduction, discussion).

EP 0346022A1 teaches an HLA-B27 restricted CTL epitope containing peptide from HIV (gag p24 265-274, KRWIILGLNKIVRMY) that can be incorporated into a vaccine against HIV, either alone or in the form of a fusion protein containing other epitopes (entire article, especially abstract, summary of the invention and claims).

Rammensee *et al* teach the minimal CTL epitope HIV-1 gag p24 265-274 (*i.e.,* KRWIILGLNK, a subsequence of that taught by EP 0346022A1 above), as well as other HIV epitopes restricted by HLA-B27 or by other class I molecules, including non-hydrophilic peptides such as SFNCGGEFF HIV gp 120 amino acid residues 380-388 (especially Table 3 on page 200, page 209, page 210, pages 193-198).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

Skidgel teaches Gly-Arg is a substrate of human plasma carboxypeptidase N (especially Table II on page 662, abstract and paragraph spanning pages 653-654).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the lipopeptide taught by WO 95/19783 A1 by using an HIV CTL epitope such as that taught by US Patent No. 5,935,824 or by Rammensee *et al* or by EP 0346022A1 for the antigenic determinant from viral protein, or to have used a cluster peptide constructed using knowledge of the overlapping HIV CTL epitope peptides taught by Rammensee *et al* (*i.e.,* one comprising GEIYKRWIILGLNK) as per the teaching of Berzofsky *et al*, to have retained the auxiliary Th epitope taught by WO 95/19783 A1 that is recognized by Th cells in the majority of the population, to have used the palmitic acid moiety taught by WO 95/19783 A1 or Deprez *et al* or one of the other single lipid moieties taught by Deprez *et al*, to have made a hydrophilic spacer comprising an arginine as disclosed by US Patent No. 5,935,824 and including the Gly

taught by WO 95/19783 A1 with the carboxypeptidase N sequence GR taught by Skidgel between the Th and the CTL epitope and between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1, and to have made a vaccine as taught by EP 0346022A1 or by Berzofsky *et al*. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have separated the CTL epitopes by interspersing a linker if more than one was to be included as per the teaching of EP 0346022A1 in order to avoid the creation of neo-epitopes or the destruction of existing epitopes.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 and Deprez *et al* teach attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1, Deprez *et al* and Berzofsky *et al* teach that the use of Th epitope in combination with a CTL epitope can also enhance elicitation of the immune response and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, *i.e.,* will be cleaved, Skidgel teaches that GR is the sequence for cleavage by human plasma carboxypeptidase N, and WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the solubility of the lipopeptide in solution because the lipid moiety is hydrophobic as was known to one of ordinary skill in the art at the time the invention was made, and even more particularly when the CTL epitope was also non-hydrophilic such as one of the peptides taught by Rammensee *et al*. In the case of the cluster peptide, one of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a vaccine that would be broadly reactive in the population as taught by Berzofsky *et al* because Berzofsky *et al* teach a vaccine comprising a cluster peptide can be broadly reactive in diverse outbred populations such as humans, and that a complete synthetic vaccine should elicit not only CTL, but Th cells and antibodies.

16. Claims 23, 30, 31, 35-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/19783 A1 (of record) in view of U.S. Patent No. 5,993,823 (of record), U.S. Patent No. 5,935,824 (of record) and Skidgel (Meth. Enzymol 1995, Vol. 248, pages 653-663).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the

time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

WO 95/19783 A1 teaches: (1) covalent attachment of palmitic acid to peptides will increase immunogenicity, (2) that attachment of Th epitopes such as the multivalent auxiliary Th epitope tetanus toxin peptide 830-843 QYIKANSKFIGITE or the PADRE peptide, which is recognized by Th cells in the majority of the population, to CTL epitopes will also increase immunogenicity, and (3) teaches that an amino acid sequence containing a Th epitope can be linked to the CTL epitope via peptide spacers of usually one to six amino acid residues that are typically neutral polar or nonpolar amino acid residues such as for example, glycine or alanine, (4) that the Th epitope may be linked at the N-terminus via a peptide spacer to the lipid, and (5) that amino acid residues such as cysteine, lysine, glutamic acid, serine or aspartic acid may be introduced at the N-terminus or the C-terminus of the peptide for modifying the physical or chemical properties of the peptide or to link peptides to one another or for coupling to a support or to another molecule (especially page 8 at lines 10-26, page 13 at lines 21-32, page 14 at lines 5-15, page 16 at lines 1-16). WO 95/19783 A1 further teaches vaccines containing the peptides or lipopeptides that can react with antigenic determinants from viral or tumor cell proteins (especially page 21 at lines 17-27). WO 95/19783 A1 teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an immunogenic tumor peptide (CTL epitope) linked to a palmitic acid lipidated Th epitope QYIKANSKFIGITE (especially claims 8, 18, 19 and 20.) WO 95/19783 A1 teaches that lysine, arginine and histidine are exemplary amino acid substutions for each other (especially page 11).

WO 95/19783 A1 does not teach wherein the CTL epitope is from HIV, nor wherein the spacer is a hydrophilic amino acid residue chain consisting of GR.

U.S. Patent No. 5,993,823 discloses that lipopeptides/vaccine compositions thereof can comprise a single lipid moiety, palmitic acid, trimexautide or cholsterol, and a sequence of between 10 and 40 amino acid residues approximately and comprising a CTL epitope from HIV, such as for example, HIV env 312-327 or 302-335. U.S. Patent No. 5,993,823 discloses that neutralizing antibodies have been obtained in mice by immunization against HIV env derived lipopeptides. U.S. Patent No. 5,993,823 further discloses that lipopeptide vaccines are safe, without side effects and easily applicable to humans. U.S. Patent No. 5,993,823 discloses association of lipopeptides inducing CTL to other lipopeptides capable to generate antibodies should result in efficient protection. U.S. Patent No. 5,993,823 discloses CTL epitope from a tumor specific protein collinear with the promiscuous (*i.e.,* multivalent auxiliary Th epitope) Th sequence KSSQYIKANSKFIGITE. U.S. Patent No. 5,993,823 discloses using the lipopeptides to treat warm-blooded animals, including humans to elicit CTL against viral or tumor proteins (see entire document, especially abstract, column 2 at lines 59-67, column 3-7 at line 18, column 46 at conclusion and claims).

US Patent No. 5,935,824 discloses fusion proteins comprising a domain comprising a hydrophilic spacer comprising either Lys or Arg (especially column 6 at lines 57-58 and the sentence spanning columns 6 and 7). US Patent No. 5,935,824 further discloses that the hydrophilic and basic nature of Arg and Lys residues causes them to be orientated within exposed regions of the fusion protein and increases the likelihood that that linker will be accessible to digestion with endoproteases (especially column 11 at lines 23-27).

Skidgel teaches Gly-Arg is a substrate of human plasma carboxypeptidase N (especially Table II on page 662, abstract and paragraph spanning pages 653-654).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the lipopeptide taught by WO 95/19783 A1 by using an HIV CTL epitope such as that taught by US Patent No. 5,935,824 or as disclosed by U.S. Patent No. 5,993,823 for the antigenic determinant from viral protein, to have retained the multivalent auxiliary Th epitope taught by WO 95/19783 A1 or disclosed by U.S. Patent No. 5,993,823, to have used the palmitic acid moiety taught by WO 95/19783 A1 or disclosed by U.S. Patent No. 5,993,823 or one of the other single lipid moieties disclosed by U.S. Patent No. 5,993,823, to have used a hydrophilic spacer comprising Arg as disclosed by US Patent No. 5,935,824 and including the Gly taught by WO 95/19783 A1 with the sequence of the substrate for human plasma carboxypeptidase N between the Th and the CTL epitope and between the Th epitope and the lipid in the lipopeptide taught by WO 95/19783 A1, and to have made a vaccine comprising the lipopeptide as disclosed by U.S. Patent No. 5,993,823. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have interposed a linker between the CTL epitope and a second CTL epitope if one was used, in order to avoid creating a neo-epitope or destroying an existing epitope.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to elicit an immune response or to improve efficacy of immunization to HIV, because WO 95/19783 A1 and U.S. Patent No. 5,993,823 teach attachment of a single lipid moiety can enhance the immune response to a CTL epitope, WO 95/19783 A1 and U.S. Patent No. 5,993,823 teach that the use of Th epitope in combination with a CTL epitope to enhance elicitation of the immune response, and that the elicitation of antibodies and Th cells is desirable in a vaccine composition, Patent No. 5,935,824 discloses using hydrophilic spacers comprising Arg to increase the likelihood that the linker will be accessible to digestion with endoproteases, *i.e.,* will be cleaved, Skidgel teaches that GR is the target sequence for human plasma carboxypeptidase N, and WO 95/19783 A1 teaches that Lys and Arg are exemplary substutions for each other.

17. Claim 23 is objected to because of the following informalities:

a. Claim 23 is objected to because it recites "aminoacid spacer." The correct spelling is 'amino acid spacer'.

b. Claim 23 is objected to because it recites "GLY ARG and ARG GLY ARG." The 3-letter amino acid code should be a capital letter followed by 2 lower-case letters, *i.e.,* Gly Arg and Arg Gly Arg.

Appropriate corrections are required.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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